

543, 117

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
16 September 2004 (16.09.2004)

PCT

(10) International Publication Number  
**WO 2004/078762 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 493/22**

(21) International Application Number:  
**PCT/KR2004/000086**

(22) International Filing Date: 19 January 2004 (19.01.2004)

(25) Filing Language: **Korean**

(26) Publication Language: **English**

(30) Priority Data:  
10-2003-0004511 23 January 2003 (23.01.2003) KR

(71) Applicant and

(72) Inventor: JUNG, Man-Kil [KR/KR]; 103-302, Samsung Apt., Namgajwa-dong, Seodaemun-gu, Seoul 120-120 (KR).

(74) Agent: NAM, Sang-Sun; 9th Fl., Maekyung Media Center, 30, 1-ga, Pil-dong, Jung-ku, Seoul 100-728 (KR).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/078762 A1

(54) Title: DEOXOARTEMISININ ANALOGS, PROCESS FOR THEIR PREPARATION, AND ANTICANCER AGENT COMPRISING THEM

(57) Abstract: The present invention relates to a new deoxoartemisinin dimer and trimer, which have excellent anticancer activity and lower toxicity and are stable to acids, to a new deoxoartemisinin monomer of intermediate thereof, to preparations thereof, and to anticancer agents comprising the deoxoartemisinin dimer or trimer.

**DEOXOARTEMISININ ANALOGS, PROCESS FOR THEIR PREPARATION,  
AND ANTICANCER AGENT COMPRISING THEM**

5

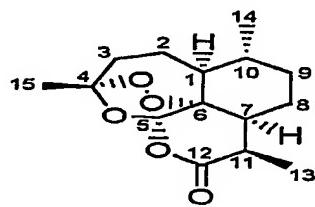
**TECHNICAL FIELD**

The invention relates to deoxoartemisinin analogs, process for their preparation and anticancer agent comprising them. More particularly, the present invention relates to a new deoxoartemisinin dimer and trimer, which have excellent anticancer activity and lower toxicity and are acid stable, to a new deoxoartemisinin monomer of intermediate thereof, to preparations thereof, and to anticancer agents comprising the deoxoartemisinin dimer or trimer.

15

**BACKGROUND ART**

Artemisinin (Qinghaosu)(I), a sesquiterpene lactone endoperoxide, is the first natural trioxane isolated from *Artemisia annua*, L.

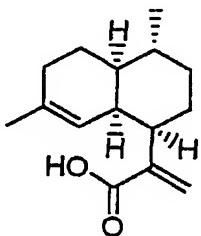


20

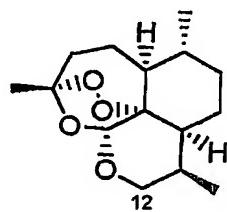
I

The artemisinin is of special biological interest because of its outstanding antimalarial activity and outstanding activity against *pneumocystis carinii* and *toxoplasma gondii*. The anti-human immunodeficiency virus (HIV) activity of artemisinin derivatives has been also reported. Artemisinin has been subjected to a number of reviews because of its novel structure and outstanding antimalarial activity. Most first generation C-12 acetal type derivatives are hydrolytically unstable. Also, most semi-syntheses have involved

replacing the C-12 acetal functionality in ether derivatives by less hydrolytically prone functional groups. Recently, however, C-12 non-acetal-type deoxoartemisinin (III) prepared from either artemisinin of formula (I) or artemisinic acid of formula (II) has been reported to show more antimalarial activity than that of artemisinin both *in vitro* and *in vivo* (see Jung, M.; Li, X.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D., A Short and Stereospecific Synthesis of (+)-Deoxoartemisinin and (-)-Deoxodesoxyartemisinin, *Tetrahedron Lett.*, 1989, 30, 5973-5976 and Jung, M.; Li, X.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D.; Milhous, W. K., Synthesis and Antimalarial Activity of (+)-Deoxoartemisinin, *J. Med. Chem.*, 1990, 33, 1516-1518).



II



III

Non-acetal-type analogs of deoxoartemisinin recently received attention owing to their better bioavailability, such as acid stability, than acetal-type analogs. Furthermore, evidence that analogs not possessing exo-oxygen at C-12 are less neurotoxic in animal studies than acetal type artemisinin is also emerging and may thus lead to the future

abandonment of the currently clinically used acetal-type analogs (e.g., arteether, artemether, artesunate and artelinic acid). After the preparation of 12-n-butyldeoxoartemisinin as the first hydrolytically stable non-acetal type analog containing a C-C bond at C-12 was reported, a series of non-acetal-type derivatives including a few of heteroaryl and unsaturated substituents at C-12 have been prepared (See Jung, M.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D., A Concise and Stereoselective Synthesis of (+)-12-n-Butyldeoxoartemisinin, *Synlett*, 1990, 743-744 and Chorki, F.; Crousse, B.; Bonnet-Delpon, D.; Begue, J. P.; Brigaud, T.; Portella, C., C-10 Fluorinated Derivatives of Dihydroartemisinin: Difluoromethylene Ketones, *Tetrahedron Lett.*, 2001, 42, 1487-1489).

Although most studies have focused on antimalarial activities, a few research groups have

recently reported on cancer cell toxicity of artemisinin and its related derivatives. (see Woerdenbag, H. J.; Moskal, T. A.; Pras, N.; Maringle, T. M.; ElFeraly, F. S.; Kampinga, H. H.; Konings, A. W. T., Cytotoxicity of Artemisinin-related Endoperoxides to Ehrlich ascites Tumor cells, *J. Nat. Prod.*, 1993, 56, 849 and Wu, J-M.; Shan F.; Wu, G-S.; Li, Y.; Ding, J.; Xiao, D.; Han, J-X.; Atassi, G; Leonce, S.; Caillard, D-H.; Renard, P., Synthesis and Cytotoxicity of Artemisinin derivatives containing Cyanoarylmethyl group, *Eur. J. Med. Chem.*, 2001, 36(5), 469-479). Because of their higher rate of cell division, most cancer cells express a higher surface concentration of transferrin receptors than normal cells and have high rates of iron intake. A unique structure bearing endoperoxide could be a trigger for the generation of active oxygen radicals via hemolytic cleavage of the weak oxygen-peroxide bond accelerated by higher ferrous ion concentration of cancer cell, which may mediate for the selective and preferable damage to vital cellular structures of the relatively active cancer cells. Although some dimers of acetal type derivatives of artemisinin have been prepared and show anticancer activities, yields are low and most of them possess either aromatic linkers or still acetal types at the C-12 position, which are neurotoxic, acid unstable, and show low anticancer activities (see Galal, A. M.; Ahmad, M. S.; El-Feraly, F. S., Preparation and Characterization of a New Artemisinin-Derived Dimer, *J. Nat. Prod.*, 1996, 59, 917-920; Posner, G. H.; Ploypradith, P.; Parker, M. H.; O'Dowd, H.; Woo, S-H.; Northrop, J.; Krasavin, M.; Dolan, P.; Kensler, T. W.; Xie, S.; Shapiro, Antimalarial, Antiproliferative, and Antitumor Activities of Artemisinin-Derived, Chemically Robust, Trioxane Dimers., *J. Med. Chem.*, 1999, 42, 4275-4280; and Ekthawatchai, S.; Kamchonwongpaisan, S.; Kongsaeree, P.; Tarnchompoon, B.; Thebtaranonth, Y.; Yuthavong, Y., C-16 Artemisinin Derivatives and Their Antimalarial and Cytotoxic Activities: Synthesis of Artemisinin Monomers, Dimers, Trimers, and Tetramers by Nucleophilic Additions to Artemisitene, *J. Med. Chem.*, 2001, 44, 4688-4695).

### DISCLOSURE

- 30 Surprisingly, we found that deoxyartemisinin dimer and trimer had excellent anticancer activity, by preparing non-acetal-type deoxyartemisinin dimer and trimer having no linker containing C-O bonds, aromatic or unsaturated groups at C-12 position and then testing the

anticancer activity thereof.

Accordingly, it is an object of the present invention to provide a deoxoartemisinin dimer and trimer having excellent anticancer activity.

5

It is another object of the present invention to easily prepare the deoxoartemisinin dimer and trimer in high yield.

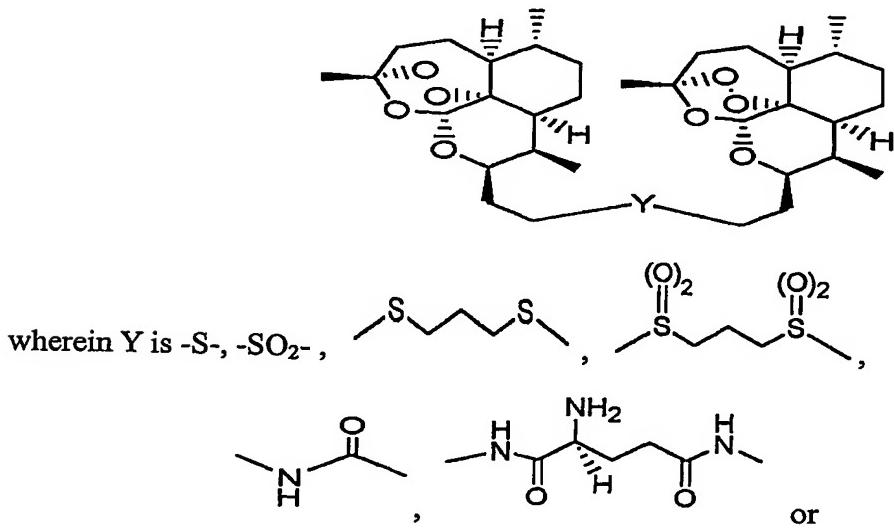
10 It is another object of the present invention to provide anticancer agents comprising the deoxoartemisinin dimer and trimer.

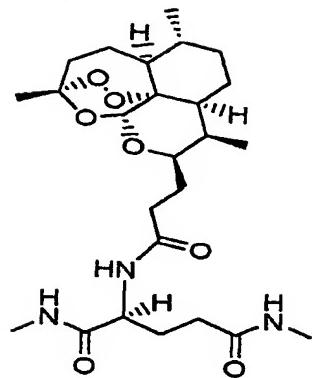
It is another object of the present invention to provide a deoxoartemisinin monomer of intermediate for preparing the deoxoartemisinin dimer and trimer in high yield.

15 It is another object of the present invention to easily prepare the deoxoartemisinin monomer in high yield.

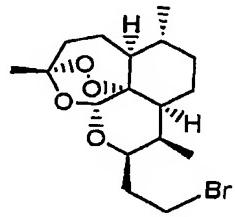
Deoxoartemisinin dimer and trimer of the present invention have the following formula (IV):

20

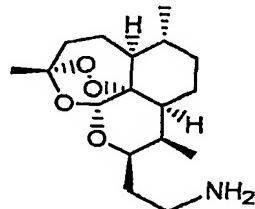




The deoxoartemisinin dimer and trimer of the present invention are prepared from the deoxoartemisinin monomers of formula (V) and (VI), respectively, as shown in Schemes 1,  
 5 2 and 3 below.



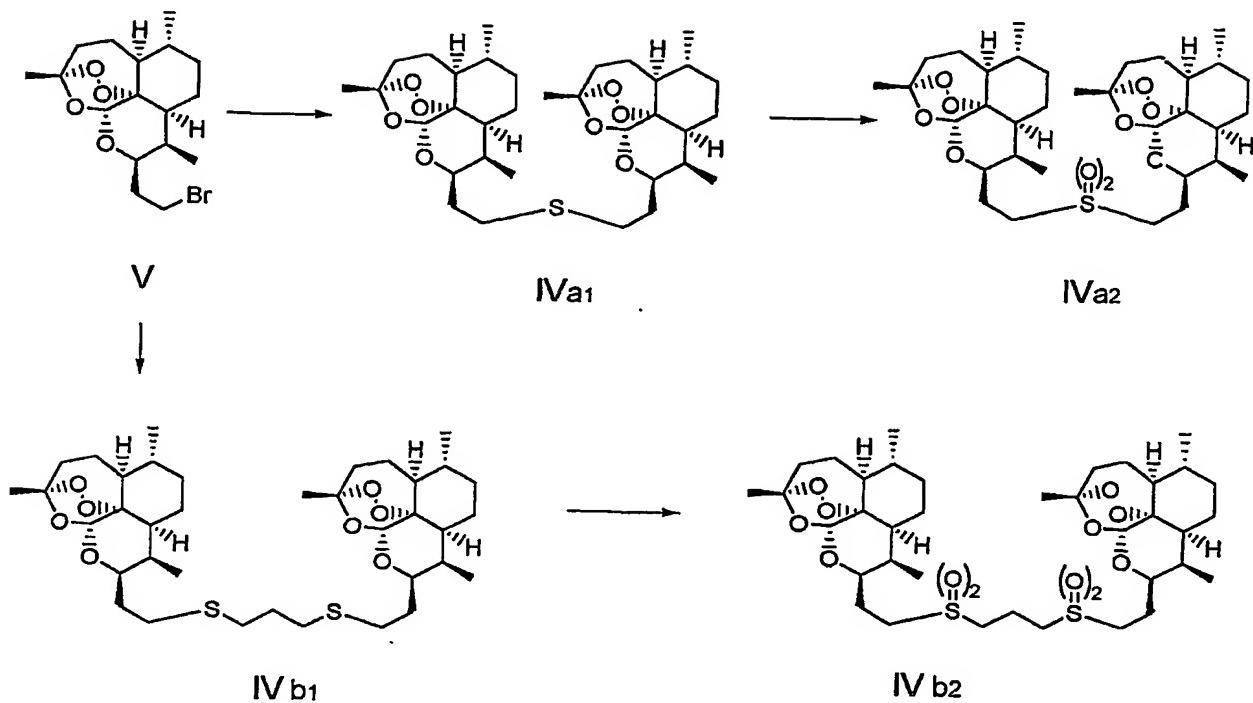
V



VI

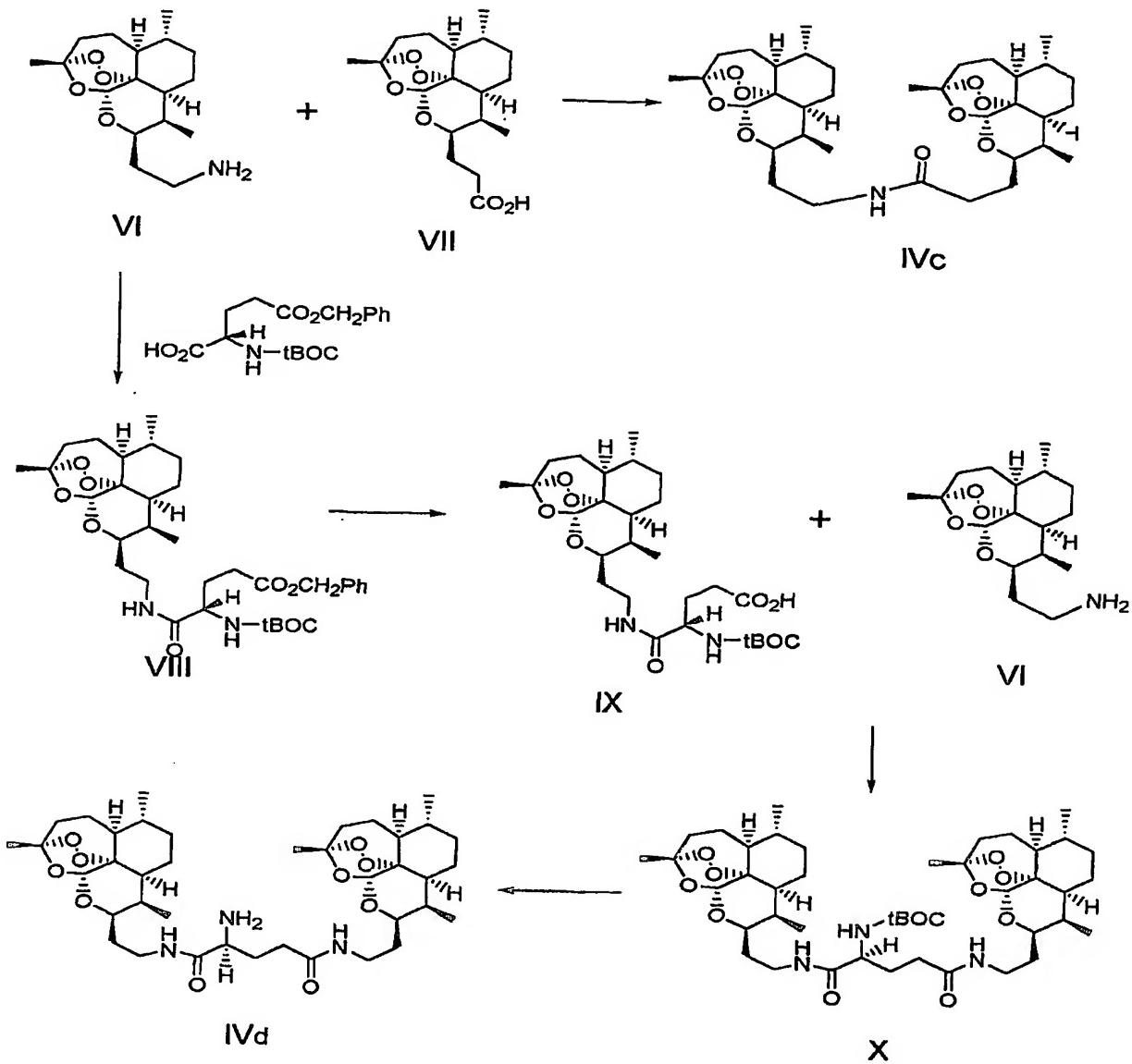
The deoxoartemisinin dimer of the present invention having sulfide- or sulfonyl  
 10 group-bearing linker is prepared by bis-nucleophilic coupling reaction of  
 12-bromoethyldeoxoartemisinin monomers (V), as shown in Scheme 1 below.  
 Particularly, the deoxoartemisinin dimer (IVa<sub>1</sub>) is prepared by reacting 1 mole of sodium  
 15 sulfide with 2 moles of 12-bromoethyldeoxoartemisinin (V) and dimer (IVa<sub>2</sub>) is prepared  
 by oxidizing the dimer (IVa<sub>1</sub>) with oxidizing agent such as meta-chloroperbenzoic acid  
 (m-CPBA). In a similar fashion, the deoxoartemisinin dimer (IVb<sub>1</sub>) is prepared by 1 mole  
 of 1,3-propanedithiol with 2 moles of 12-bromoethyldeoxoartemisinin (V) and the dimer  
 (IVb<sub>2</sub>) is prepared by reacting the dimer (IVb<sub>1</sub>) with an oxidizing agent such as m-CPBA.

Scheme 1



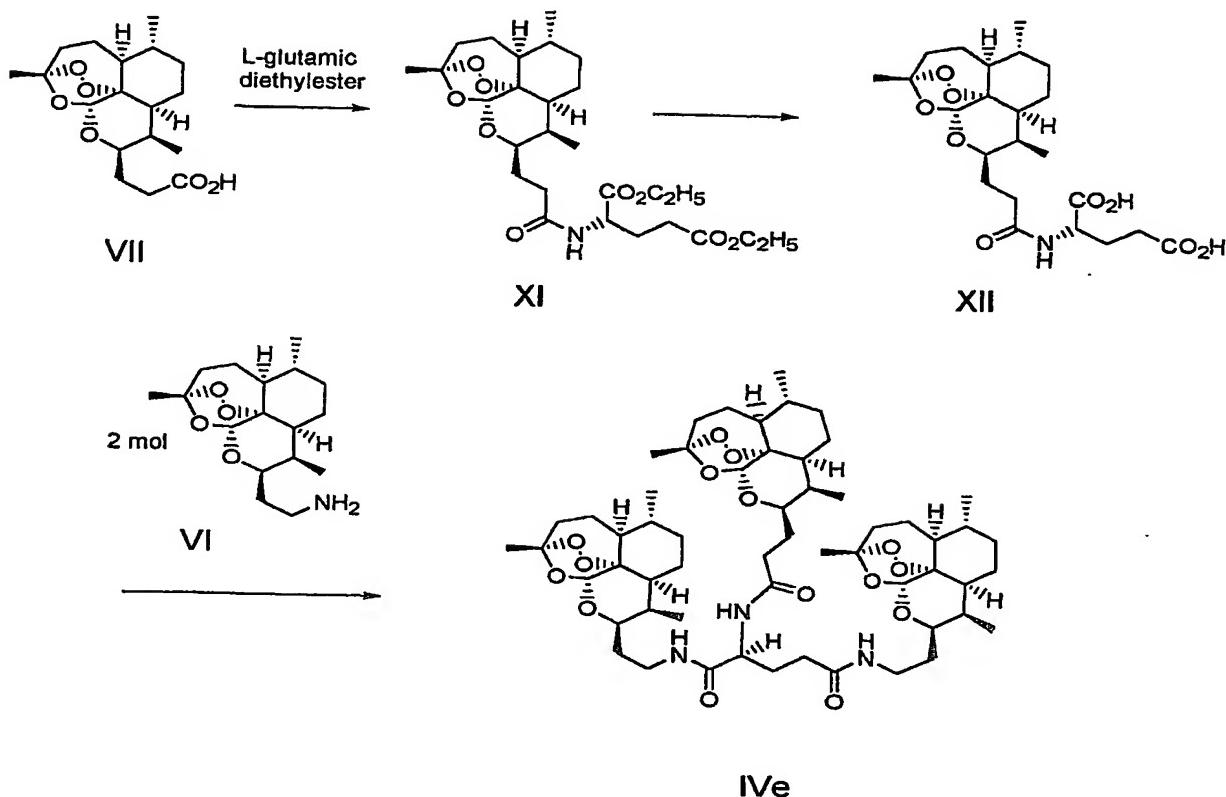
- 5 The deoxoartemisinin dimer of the present invention having amide groups-containing  
linker is prepared from 12-aminoethyldeoxoartemisinin (VI), as shown in Scheme 2 below.  
Particularly, the deoxoartemisinin dimer (IVc) is prepared by coupling  
12-aminoethyldeoxoartemisinin (VI) with 12-carboxylethyldeoxoartemisinin (VII) in the  
presence of a catalyst such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(EDC)/10-hydroxybenzotriazole(HOBt).  
10 On the other hand, the deoxoartemisinin dimer (IVd) is prepared by directly coupling  
12-aminoethyldeoxoartemisinin (VI) with protected glutarate in the presence of a catalyst  
such as EDC/HOBt, removing the benzyl group of the ester, coupling the resultant product  
with 12-aminoethyldeoxoartemisinin (VI) in the presence of a catalyst such as EDC/HOBt  
and then deprotecting the t-BOC protected group of the amino group of the resultant  
15 product.

Scheme 2



The deoxoartemisinin trimer (IVe) of the present invention is prepared by coupling 5 12-carboxylethyldeoxoartemisinin (VII) with L-glutamic diethylester in the presence of a catalyst such as EDC/HOBt, hydrolyzing the two ester groups of the product from the previous step and then doubly coupling the product from the previous step with 2 moles of 12-aminoethyldeoxoartemisinin (VI) in the presence of a catalyst such as EDC/HOBt, as shown in Scheme 3 below.

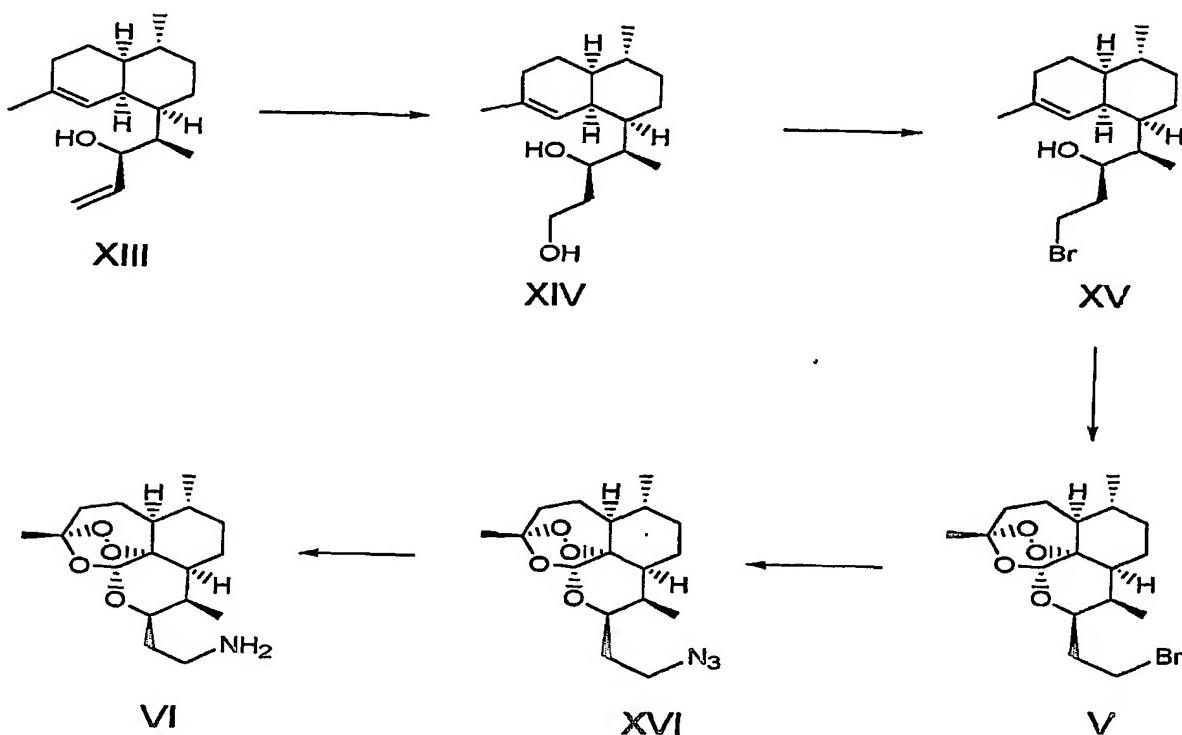
Scheme 3



The novel deoxoartemisinin monomers (V and VI), which are intermediates for preparing  
 5 the deoxoartemisinin dimer and trimer of the present invention, are prepared from  
 12-vinyldihydroartemisinyl alcohol (XIII), as shown in Scheme 4 below. A  
 12-vinyldihydroartemisinyl alcohol (XIII) can be synthesized from artemisinic acid (II) by  
 a known synthetic route (see Jung et al., A Concise and Stereoselective Synthesis of  
 (+)-12-n-Butyldeoxoartemisinin, *Synlett*, 1990, 743-744). Since artemisinin is much  
 10 more expensive than artemisinic acid and a direct introduction of a C-C bond at C-12 of  
 artemisinin may cause a destruction of the biologically essential endoperoxide, the  
 artemisinic acid is used. Particularly, 12-bromoethyldeoxoartemisinin (V) is prepared by  
 direct hydroborative oxidizing a terminal olefin of 12-vinyldihydroartemisinyl alcohol  
 (XIII), brominating the resultant product with  $\text{CBr}_4/\text{PPh}_3$ , photooxygenative cyclizing the  
 15 resultant product by a known procedure (see Jung, M et al., *supra*). On the other hand,  
 12-aminoethyldeoxoartemisinin (VI) is prepared by reacting  
 12-bromoethyldeoxoartemisinin (V) with sodium azide and then reducing the azide of the

resultant product. In the preparation of 12-bromoethyldeoxoartemisinin (V) and 12-aminoethyldeoxoartemisinin (VI) according to the above-mentioned procedures, 12 $\beta$ -epimer is obtained exclusively.

5 Scheme 4



The deoxoartemisinin dimer and trimer of the present invention is C-12 non-acetal-type and have no linker containing C-O bonds, aromatic or unsaturated groups at C-12 position, and thus is less neurotoxic, acid stable and have a higher anticancer activity. Therefore, the dimer and trimer of the present invention can be used as an effective anticancer agent for oral administration.

An anticancer agent containing the deoxoartemisinin dimer or trimer of the present invention as an effective constituent can be administered orally (e.g., ingestion or inhalation) or parenterally (e.g., intravenous injection, subcutaneous injection, percutaneous absorption, etc.) and can be prepared in the various form of tablets, capsules, granules, fine subtilae, powders, sublingual tablets, suppositories, ointments, injections,

emulsions, suspensions, drug-treated syrups, etc., depending on its use. The above-mentioned various type of anticancer agents are prepared by a known technique using pharmaceutically acceptable conventional carrier such as excipient, binder, disintegrator, lubricant, antiseptic, antioxidant, isotonic agent, buffer, coating, sweetening,  
5 solubilizer, base, dispersion, stabilizer, colorant.

In the preparation of the agent, the content of the compounds of the present invention depends on the type of agents, but preferably ranges from 0.01 to 100% by weight.

10 The dosage of the anticancer agent of the present invention will vary depending on a variety of factors, such as, the kind of mammalian including human to be treated, the severity of the disease and the physician's judgment. Typically, for oral administration, the anticancer agent of the present invention can be administered as an effective constituent in the amount of 0.01 to 50mg per kg body weight per day and, for parenteral  
15 administration, in the amount of 0.01 to 10mg per kg body weight per day.

The anticancer agent of the present invention can be administered at one time or at several times per day and its dosage can be varied depending on the severity of the disease and the physician's judgment.

20

The present invention is further described in the following examples. These examples illustrate the invention only and are not to be construed as limiting the scope of the present invention in any way.

25

### EXAMPLES

#### **Example 1: Synthesis of 12-(2'-bromoethyl)deoxoartemisinin (V)**

30

(1) Synthesis of 12-(2'-hydroxyethyl)dihydroartemisinyl alcohol (XIV).

12-vinyldihydroartemisinyl alcohol (XIII)(568mg, 2.290mmol), prepared by a known procedure (see Jung et al., A Concise and Stereoselective Synthesis of (+)-12-n-Butyldeoxoartemisinin, *Synlett*, 1990, 743-744), was slowly added to THF solution containing 0.5M of 9-borabicyclo[3.3.1]nonan(9BBN)(9.1mL, 4.58mmol) under 5 nitrogen atmosphere and the resulting mixture was stirred at room temperature for 30minutes. Then, to this solution was added 30%-H<sub>2</sub>O<sub>2</sub>/3N-NaOH(1/1, 2mL) and the resulting solution was stirred at room temperature for 1hour. The reaction mixture was extracted with ether (40mL x 2) and washed with saturated NaHCO<sub>3</sub>(20mL) and brine (20mL x 2). The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo and purified by 10 silica gel column (hexane/ethyl acetate = 1/1 as eluent) to afford 12-(2'-hydroxyethyl)dihydroartemisinyl alcohol (XIV) as a colorless oil (97% yield).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz) δ5.15(s, 1H, H-5), 4.14(d, 1H, *J*=9.8Hz, H-12), 3.89-3.80(m, 2H, H-2), 2.47(s, 1H), 1.94-1.72(m, 6H), 1.54(s, 3H, CH<sub>3</sub>-15), 1.53-1.25(m, 9H), 0.84(d, 15 3H, *J*=7.3Hz, CH<sub>3</sub>-13), 0.87(d, 3H, *J*=6.6Hz, CH<sub>3</sub>-14).

<sup>13</sup>C-NMR(CDCl<sub>3</sub>, 63MHz) δ135.5, 120.9, 72.0, 62.6, 42.6, 42.5, 39.7, 37.8, 37.6, 36.0, 28.1, 27.0, 26.4, 26.2, 24.1, 20.1, 10.4.

IR(neat)  $\nu_{max}$  3435(OH), 2921, 1647, 1622, 1386, 1124, 1088, 1016 cm<sup>-1</sup> MS(EI) m/z 266([M+]), 248([M+]-H<sub>2</sub>O), 203([M+]-C<sub>2</sub>H<sub>5</sub>O).

20

(2) Synthesis of 12-(2'-bromoethyl)dihydroartemisinyl alcohol (XV).

12-(2'-hydroxyethyl)dihydroartemisinyl alcohol (XIV) (399mg, 1.503mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub>(20mL) and triphenylphosphine (TPP)(393mg, 1.503mmol) was added. 25 The solution was allowed to stir at 0°C for 30minutes. The reaction mixture was warmed to room temperature. To this reaction mixture was slowly added CBr<sub>4</sub> (498mg, 1.503mmol). The reaction was allowed to stir at room temperature for 30minutes and was quenched with methanol (10mL). The reaction mixture was extracted with ethyl acetate (20mL x 3) and was washed with brine (20mL x 2). The extract was dried over 30 MgSO<sub>4</sub>, concentrated in vacuo and purified by silica gel column (hexane/ethyl acetate = 5/2 as eluent) to afford 12-(2'-bromoethyl)dihydroartemisinyl alcohol (XV)(470mg, 95%)

as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, 250MHz) δ5.14(s, 1H, H-5), 4.1(d, 1H, J=7.5Hz, H-12), 3.57-3.52(t, 2H, J=7.5Hz), 2.31(s, 1H), 1.94-1.71(m, 6H), 1.54(s, 3H, CH<sub>3</sub>-15), 1.53-1.25(m, 9H), 0.84(d, 5 6H, J=5.0Hz, CH<sub>3</sub>-13,14).

<sup>13</sup>C-NMR(CDCl<sub>3</sub>, 63MHz) δ135.5, 120.7, 69.8, 42.8, 42.4, 39.1, 38.9, 37.8, 36.0, 31.9, 28.0, 27.0, 26.4, 26.1, 24.1, 20.1, 10.2.

IR(neat) ν<sub>max</sub> 3427(OH), 2910, 1726, 1447, 1378, 1259, 992, 908, 734 cm<sup>-1</sup>

MS(EI) m/z 328([M+]), 310([M+]-H<sub>2</sub>O), 249([M+]-Br).

10

(3) Synthesis of the title compound

12-(2'-bromoethyl)dihydroartemisinyl alcohol (XV)(250mg, 0.665mmol) was added to CH<sub>3</sub>CN/CH<sub>2</sub>Cl<sub>2</sub> (1/1, 60mL) containing catalytic Rose Bengal and then was irradiated with

15 white light (500W tungsten lamp) at -23 °C for 4hours under oxygen. After completion of the reaction, to the reaction mixture was added saturated NaHCO<sub>3</sub> solution (50mL). This mixture was extracted with diethyl ether (20mL x 3) and then washed with brine (20mL x 2). The extract was dried over MgSO<sub>4</sub>. Solvent was evaporated under reduced pressure and the residue was dissolved in CH<sub>3</sub>CN/CH<sub>2</sub>Cl<sub>2</sub>(9/1, 10mL). This solution was

20 cooled to -40 °C. Acidic catalyst trifluoroacetic acid (TFA) was added to this solution and then was allowed to stir at -40 °C for 12hours under oxygen. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution (10mL) and extracted with diethyl ether (20mL x 3).

25 The extract was washed with water (30mL x 2) and brine (30mL x 2), dried over MgSO<sub>4</sub>, concentrated in vacuo and purified by silica gel column (hexane/ethyl acetate = 5/1 as eluent) to afford 12-(2'-bromoethyl)deoxoartemisinin (V)(99mg, 40%) as a white solid.

[α]<sup>18</sup><sub>D</sub> = +96.3(c 0.1, CHCl<sub>3</sub>).

m.p. 94 °C.

30 <sup>1</sup>H-NMR(CDCl<sub>3</sub>, 500MHz) δ5.26(s, 1H, H-5), 4.33-4.27(m, 1H, H-12), 3.56-3.51(m, 2H, H-2'), 2.60-2.45(m, 2H), 2.30(ddd, 1H, J=4.1, 3.8, 4.1Hz), 2.05-1.89(m, 4H), 1.83-1.48(m,

4H), 1.39(s, 3H, CH<sub>3</sub>-15), 1.28-1.22(m, 2H), 0.94(d, 3H, J=4.8Hz, CH<sub>3</sub>-13), 0.87(d, 3H, J=7.4Hz, CH<sub>3</sub>-14), 0.78(m, 1H).

<sup>13</sup>C-NMR(CDCl<sub>3</sub>, 125MHz) δ103.4, 89.5, 81.2, 73.2, 52.4, 44.4, 37.7, 37.3, 35.8, 34.8, 33.7, 31.6, 30.3, 26.3, 25.0, 20.4, 13.1.

- 5 IR(KBr) υ<sub>max</sub> 2950, 1451, 1377, 1272, 1117, 1042, 1010, 880(O-O), 756 cm<sup>-1</sup>  
MS(EI) m/z 376(M+2), 342([M+]-O<sub>2</sub>).

**Example 2: Synthesis of 12-(2'-aminoethyl)deoxoartemisinin (VI).**

- 10 (1) Synthesis of 12-(2'-ethyl azide)deoxoartemisinin (XVI).

12-(2'-bromoethyl)deoxoartemisinin (V)(128mg,0.352mmol) was dissolved in DMF(5mL) and sodium azide (45.7mg, 0.704mmol) was added. This mixture was allowed to stir at room temperature for 5hours. To the reaction mixture was added water (30mL). The 15 resulting mixture was extracted with ethyl acetate (50mL x 2) and then washed with brine (40mL x 2). The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo, then purified by silica gel column (hexane/ethyl acetate = 5/2 as eluent) to afford 12-(2'-ethyl azide)deoxoartemisinin (XVI)(109mg, 92%) as a colorless oil.

- 20 [α]<sup>23</sup><sub>D</sub> = +64.2(c 0.47, CHCl<sub>3</sub>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz) δ5.28(s, 1H, H-5), 4.31-4.27(m, 1H, H-12), 3.56-3.53(m, 1H), 3.44-3.38(m, 1H), 2.69-2.64(m, 1H), 2.31(ddd, 1H, J=4.1, 3.8, 4.1Hz), 2.03-1.75(m, 5H), 1.67-1.60(m, 3H), 1.40(s, 3H, CH<sub>3</sub>-15), 1.33-1.27(m, 3H), 0.96(d, 3H, J=5.6Hz, CH<sub>3</sub>-13), 0.87(d, 3H, J=7.5Hz, CH<sub>3</sub>-14), 0.82(m, 1H).

- 25 <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63MHz) δ103.5, 89.5, 81.3, 72.3, 52.5, 49.8, 44.5, 37.8, 36.9, 34.7, 30.4, 29.5, 26.3, 25.1, 25.1, 20.4, 13.1.

IR(neat) υ<sub>max</sub> 2927, 2875, 2095(N<sub>3</sub>), 1733, 1454, 1377, 1277, 1098, 1011, 880(O-O), 756 cm<sup>-1</sup>

MS(EI) m/z 337[M+], 305([M+]-O<sub>2</sub>).

30

(2) Synthesis of the title compound.

12-(2'-ethylazide)deoxoartemisinin (XVI)(137.9mg, 0.352mmol) was dissolved in dry THF(10mL), cooled to -78 °C and LAH(35.1mg, 0.925mmol) was added. The solution was allowed to stir at -78 °C for 1hour, warmed to -10 °C slowly and allowed to stir at that temperature for 1hour. The reaction mixture was extracted with ethyl acetate (50mL x 2) and washed with brine (40mL x 2). The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo, then purified by silica gel column (100% methanol as eluent) to afford 12-(2'-aminoethyl)deoxoartemisinin (VI)(85.4mg, 78%) as a white solid.

[α]<sup>23</sup><sub>D</sub> = +38.7 (c 0.1, CHCl<sub>3</sub>).

10

m.p. 103 °C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz) δ5.32(s, 1H, H-5), 4.29-4.21(m, 1H, H-12), 2.93-2.84(m, 3H), 2.69-2.64(m, 1H), 2.32(ddd, 1H, J=4.0, 3.7, 4.0Hz), 2.05-1.82(m, 3H), 1.80-1.74(m, 2H), 1.62-1.50(m, 2H), 1.40(s, 3H, CH<sub>3</sub>-15), 1.32-1.26(m, 4H), 0.96(d, 3H, J=5.7Hz, CH<sub>3</sub>-13), 0.87(d, 3H, J=7.5Hz, CH<sub>3</sub>-14), 0.83(m, 1H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63MHz) δ103.5, 89.4, 81.5, 74.2, 52.7, 44.7, 41.0, 37.8, 36.9, 34.8, 33.2, 30.6, 26.5, 25.1, 25.0, 20.5, 13.4.

IR(KBr)  $\nu_{max}$  3365(NH), 2924, 2874, 1663, 1570, 1455, 1377, 1114, 1054, 1011, 944, 877(O-O), 753 cm<sup>-1</sup>

20 HRMS(FAB) m/z 312.2175([M+H]<sup>+</sup>, obsd), 311.2097(calcd for C<sub>17</sub>H<sub>29</sub>NO<sub>4</sub>).

Elemental analysis (C<sub>17</sub>H<sub>29</sub>NO<sub>4</sub>) C, H, N.

### Example 3: Synthesis of 12-(2'-ethylsulfide)deoxoartemisinin dimer (IVa<sub>1</sub>).

25

12-(2'-bromoethyl)deoxoartemisinin (V)(45mg, 0.124mmol) was dissolved in pure ethanol (4mL), allowed to stir at room temperature for 10 minutes and Na<sub>2</sub>S(4.8mg, 0.5eq) was added. The reaction mixture was allowed to stir at room temperature for 7hours. This reaction mixture was extracted with ethyl acetate (10mL x 3) and washed with brine (10mL x 2). The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo, then purified by silica gel column (hexane/ethyl acetate = 5/1 as eluent) to afford

12-(2'-ethylsulfide)deoxoartemisinin dimer (IVa<sub>1</sub>)(58.7mg, 76%) as a colorless oil.

$[\alpha]^{25}_D = +58.7$  (c 0.23, CHCl<sub>3</sub>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz) δ5.29(s, 2H, H-5), 4.24-4.19(m, 2H, H-12), 2.91-2.84(m, 2H), 5 2.71-2.70(m, 2H), 2.55-2.49(m, 2H), 2.33(ddd, 2H, J=3.1, 3.5, 4.0Hz), 2.03-1.78(m, 8H), 1.67-1.55(m, 10H), 1.41(s, 6H, CH<sub>3</sub>-15), 1.36-1.26(m, 4H), 0.96(d, 6H, J=5.8Hz, CH<sub>3</sub>-13), 0.88(d, 6H, J=7.4Hz, CH<sub>3</sub>-14), 0.83(m, 2H).

<sup>13</sup>C-NMR (63MHz, CDCl<sub>3</sub>) δ 103.6, 89.2, 81.4, 76.8, 75.5, 52.7, 44.8, 37.7, 36.9, 34.8, 30.5, 30.1, 26.5, 25.2, 25.0, 20.6, 13.5.

10 IR(neat) ν<sub>max</sub> 2925, 2876, 1617, 1459, 1379, 1119, 1054, 1011, 887(O-O), 735 cm<sup>-1</sup>

HRMS(FAB) m/z 645.3541([M+Na]<sup>+</sup>, obsd), 622.3539(calcd for C<sub>34</sub>H<sub>54</sub>O<sub>8</sub>S).

Elemental analysis (C<sub>34</sub>H<sub>54</sub>O<sub>8</sub>S) C, H, S.

#### Example 4: Synthesis of 12-(2'-sulfonylethyl)deoxoartemisinin dimer (IVa<sub>2</sub>).

15

12-(2'-ethylsulfide)deoxoartemisinin dimer (IVa<sub>1</sub>)(28mg, 0.041mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub>(2mL), allowed to stir at room temperature for 10 minutes and m-CPBA(15.7mg, 0.091mmol) was added slowly. The reaction mixture was allowed to stir at room temperature for 3h and saturated NaHCO<sub>3</sub> solution (3mL) was added. The reaction mixture was extracted with ethyl acetate (10mL x 3) and washed with brine (10mL x 2). The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo, then purified by silica gel column (hexane/ethyl acetate = 2/1 as eluent) to afford 20 12-(2'-sulfonylethyl)deoxoartemisinin dimer (IVa<sub>2</sub>)(24.6mg, 91%) as a white solid.

25  $[\alpha]^{20}_D = +84.2$  (c 0.44, CHCl<sub>3</sub>).

m.p. 98 °C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz) δ5.30(s, 2H, H-5), 4.25-4.18(m, 2H, H-12), 3.53-3.41(m, 2H, H-2), 3.05-2.935(m, 2H, H-2), 2.79-2.71(m, 2H), 2.36(ddd, 2H, J=3.2, 3.5, 4.1Hz), 2.17-1.92(m, 6H), 1.88-1.78(m, 4H), 1.69-1.49(m, 8H), 1.39(s, 6H, CH<sub>3</sub>-15), 0.97(d, 6H, 30 J=5.7Hz, CH<sub>3</sub>-13), 0.92(d, 6H, J=7.6Hz, CH<sub>3</sub>-14), 0.89(m, 2H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 63MHz) δ134.1, 130.6, 130.1, 128.6, 103.6, 89.4, 81.4, 74.1, 52.5, 44.4,

36.8, 30.5, 26.4, 25.2, 22.4, 20.4, 13.2.

IR(KBr)  $\nu_{\text{max}}$  2928, 2876, 1723, 1575, 1449, 1380, 1280, 1123, 1052, 880(O-O), 734 cm<sup>-1</sup>

HRMS(FAB) m/z 677.3335([M+Na]<sup>+</sup>, obsd), 654.3438(calcd for C<sub>34</sub>H<sub>64</sub>O<sub>10</sub>S).

Elemental analysis (C<sub>34</sub>H<sub>64</sub>O<sub>10</sub>S) C, H, S.

5

**Example 5: Synthesis of S,S'-[12-(2'-ethyl)deoxoartemisinin]dithiopropane dimer (IVb<sub>1</sub>).**

Powdered KOH(12.36mg, 0.22mmol) was added to DMSO(2mL), allowed to stir at room  
10 temperature for 1hour and then 1,3-propanedithiol(6.64 $\mu$ L, 0.054mmol) and 12-(2'-bromoethyl)deoxoartemisinin(V)(41mg, 0.112mmol) was added together. The reaction mixture was allowed to stir at room temperature for 1hour. The reaction mixture was extracted with ethyl acetate (30mL x 3) and washed with brine (20mL x 2). The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo, then purified by silica gel  
15 column(hexane/ethyl acetate = 5/2 as eluent) to afford S,S'-[12-(2'-ethyl)deoxoartemisinin]dithiopropane dimer(IVb<sub>1</sub>)(50.7mg, 65%) as a colorless oil.

[ $\alpha$ ]<sup>24</sup><sub>D</sub> = +112.3(c 0.4, CHCl<sub>3</sub>).

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz)  $\delta$  5.29(s, 2H, H-5), 4.22-4.17(m, 2H, H-12), 2.83-2.66(m, 10H), 2.41-2.29(m, 2H), 2.05-1.76(m, 10H), 1.66-1.53(m, 10H), 1.41(s, 6H, CH<sub>3</sub>-15), 1.33-1.26(m, 4H), 0.96(d, 6H, J=5.7Hz, CH<sub>3</sub>-13) 0.88(d, 3H, J=7.5Hz, CH<sub>3</sub>-14), 0.83(m, 2H).

25 <sup>13</sup>C-NMR(CDCl<sub>3</sub>, 63MHz)  $\delta$  103.6, 89.3, 81.4, 75.3, 52.7, 44.7, 38.8, 37.8, 36.9, 34.8, 32.2, 30.5, 30.2, 29.1, 26.5, 25.2, 25.0, 20.5, 13.4.

IR(neat)  $\nu_{\text{max}}$  2928, 2873, 1655, 1719, 1452, 1378, 1215, 1120, 1036, 877(O-O), 755 cm<sup>-1</sup>

HRMS(FAB) m/z 719.3701([M+Na]<sup>+</sup>, obsd) 696.3730(calcd for C<sub>37</sub>H<sub>60</sub>O<sub>8</sub>S<sub>2</sub>).

Elemental analysis (C<sub>37</sub>H<sub>60</sub>O<sub>8</sub>S<sub>2</sub>) C, H, S.

30 **Example 6: Synthesis of S,S'-[12-(2'-ethyl)deoxoartemisinin]disulfonylpropane dimer (IVb<sub>2</sub>).**

S,S'-[12-(2'-ethyl)deoxoartemisinin]disulfonylpropane dimer (IVb<sub>2</sub>)(22.6mg, 72%) as a white solid was prepared by following the procedure of Example 4, but replacing 12-(2'-ethylsulfide)deoxoartemisinin dimer (IVa<sub>1</sub>) with

5 S,S'-[12-(2'-ethyl)deoxoartemisinin]dithiopropane dimer (IVb<sub>1</sub>)(29mg, 0.041 mmol) and using 31.1mg of m-CPBA (0.18mmol).

$[\alpha]^{25}_D = +110.4(c\ 0.47, \text{CHCl}_3)$ .

m.p. 138 °C.

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz) δ5.30(s, 2H, H-5), 4.25-4.21(m, 2H, H-12), 3.49-3.43(m, 2H), 3.26(t, 2H, J=7.1Hz), 3.04-2.92(m, 2H), 2.74-2.62(m, 2H), 2.49-2.43(m, 2H), 2.41-2.29(m, 2H), 2.08-1.94(m, 8H), 1.89-1.75(m, 4H), 1.69-1.59(m, 8H), 1.39(s, 6H, CH<sub>3</sub>-15), 1.34-1.27(m, 4H), 0.97(d, 6H, J=5.7Hz, CH<sub>3</sub>-13), 0.91(d, 6H, J=7.6Hz, CH<sub>3</sub>-14), 0.88(m, 2H).

15 <sup>13</sup>C-NMR(CDCl<sub>3</sub>, 63MHz) δ134.2, 130.6, 130.1, 128.4, 103.6, 89.5, 81.4, 74.1, 52.5, 44.3, 37.7, 36.8, 34.7, 31.3, 30.5, 26.4, 25.2, 20.4, 13.5.

IR(KBr)  $\nu_{max}$  2926, 2875, 1720, 1584, 1495, 1387, 1310, 1130, 1052, 877(O-O), 756, 465 cm<sup>-1</sup>

HRMS(FAB) m/z 783.3538([M+Na]<sup>+</sup>, obsd), 760.3526(calcd for C<sub>37</sub>H<sub>60</sub>O<sub>12</sub>S<sub>2</sub>).

20 Elemental analysis (C<sub>37</sub>H<sub>60</sub>O<sub>12</sub>S<sub>2</sub>) C, H, S.

#### Example 7: Synthesis of 12-(2'-amidethyl)deoxoartemisinin dimer (IVc).

25 12-carboxylethyldeoxoartemisinin (VII)(32mg, 0.086mmol), prepared by a known procedure (see Jung, M.; Freitas, A. C. C.; McChesney, J. D.; ElSohly, H. N., A Practical and General Synthesis of (+)-Carboxyalkyldeoxoartemisinins, *Heterocycles*. 1994, 39, 23-29), was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub>(3mL) and HOEt(38mg, 0.256mmol) and EDC(47mg, 0.256mmol) was added together. The reaction mixture was allowed to stir at room

30 temperature for 30 minutes and 12-(2'-aminoethyl)deoxoartemisinin (VI)(30mg, 0.096mmol) was added. The resulting reaction mixture was allowed to stir at room

temperature for 4hours. The reaction mixture was extracted with ethyl acetate (20mL x 3) and washed with brine (10mL x 2). The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo, then purified by silica gel column (hexane/ethyl acetate = 1/2 as eluent) to afford 12-(2'-aminoethyl)deoxoartemisinin dimer(IVc) in 81% yield as a colorless oil.

5

[ $\alpha$ ]<sup>23</sup>D = +111.3 (c 0.38, CHCl<sub>3</sub>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500MHz) δ 6.28(s, 1H, NH), 5.30(s, 1H, H-5), 5.29(s, 1H, H-5), 4.33-4.31(m, 1H, H-12), 4.06-4.04(m, 1H, H-12), 3.58-3.56(m, 1H, H-2), 3.28-3.26(m, 1H, H-2), 2.73-2.69(m, 1H), 2.65-2.62(m, 1H), 2.51-2.44(m, 1H), 2.35-2.32(t, 2H, J=13.5Hz), 2.24-2.15(m, 1H), 2.04-1.98(m, 2H), 1.95-1.89(m, 3H), 1.78-1.71(m, 4H), 1.66-1.64(m, 4H), 1.40(s, 6H, CH<sub>3</sub>-15), 1.37-1.24(m, 9H), 0.96(d, 3H, J=5.3Hz, CH<sub>3</sub>-13), 0.95(d, 3H, J=5.7Hz, CH<sub>3</sub>-13), 0.88(d, 3H, J=7.5Hz, CH<sub>3</sub>-14), 0.86(d, 3H, J=7.5Hz, CH<sub>3</sub>-14), 0.84(m, 2H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63MHz) δ 173.8, 126.8, 126.1, 118.0, 111.2, 103.7, 103.5, 89.6, 89.0, 81.5, 81.4, 76.4, 74.7, 52.8, 52.5, 44.8, 44.3, 37.8, 37.6, 36.8, 35.1, 34.8, 34.7, 30.7, 30.5, 26.5, 26.4, 25.4, 25.1, 25.0, 20.5, 20.4, 13.7, 13.6.

IR(neat)  $\nu_{max}$  3380(NH), 2941, 2877, 1653(C=O), 1545, 1446(C-N), 1379, 1097, 1051, 1013, 915, 878(O-O), 733 cm<sup>-1</sup>

HRMS(FAB) m/z 634.3995([M+H]<sup>+</sup>, obsd), 633.3877(calcd for C<sub>35</sub>H<sub>55</sub>NO<sub>9</sub>).

20 Elemental analysis (C<sub>35</sub>H<sub>55</sub>NO<sub>9</sub>) C, H, N.

**Example 8: Synthesis of 12-[2'-(N-glutamic)- α , β -amide]deoxoartemisinin dimer (IVd).**

25 (1) Synthesis of 12-[2'-(N-tBOC-glutamic- γ -benzylester)- α -amide]deoxoartemisinin (VIII).

N-tBOC-L-glutamic acid- γ -benzylester(35mg, 0.11mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub>(5mL) and HOBr(52mg, 0.342mmol) and EDC(63mg, 0.342mmol) was added.

30 The reaction mixture was allowed to stir at room temperature for 30 minutes and 12-(2'-aminoethyl)deoxoartemisinin (VI)(42mg, 0.135mmol) was added. The resulting

reaction mixture was allowed to stir at room temperature for 3hours. The reaction mixture was extracted with ethyl acetate (20mL x 3) and washed with brine (10mL x 2). The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo, then purified by silica gel column (hexane/ethyl acetate = 1/2 as eluent) to afford 12-[2'-(N-tBOC-glutamic- γ -benzylester)- α -amide]deoxoartemisinin (VIII) (71.5mg, 84%) as a colorless oil.

5 [α]<sup>25</sup><sub>D</sub> = +73.6 (c 0.47, CHCl<sub>3</sub>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz) δ7.36(s, 5H, aromatic H), 7.02(br, 1H, NH), 5.33(s, 1H, H-5), 5.11(s, 2H, benzyl), 4.40-4.39(m, 1H, H-12), 4.29-4.27(m, 1H), 4.15-4.13(m, 1H), 3.58-3.56(m, 1H, H-2), 3.28-3.24(m, 1H, H-2), 2.61-2.43(m, 3H), 2.36-2.14(m, 3H), 2.12-1.98(m, 4H), 1.91-1.65(m, 4H), 1.44(s, 9H, t-BOC), 1.42(s, 3H, CH<sub>3</sub>-15), 1.35-1.26(m, 3H), 0.96(d, 3H, J=5.6Hz, CH<sub>3</sub>-13), 0.85(d, 3H, J=7.6Hz, CH<sub>3</sub>-14), 0.82(m, 1H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63MHz) δ173.2, 171.5, 155.2, 136.1, 128.8, 128.8, 128.5, 128.5, 128.4, 128.4, 103.8, 89.9, 81.3, 74.4, 66.6, 61.2, 53.1, 52.3, 44.0, 39.4, 37.7, 36.7, 34.6, 30.8, 28.6, 28.5, 28.5, 26.2, 25.1, 25.0, 20.4, 12.6.

IR(neat) ν<sub>max</sub> 3364(NH), 2932, 2876, 1736(C=O), 1663(C=O), 1538, 1453, 1393, 1249, 1163, 1051, 880(O-O), 702, 610 cm<sup>-1</sup>

HRMS(FAB) m/z 631.3507([M+H]<sup>+</sup>, obsd), 630.3516(calcd for C<sub>34</sub>H<sub>50</sub>N<sub>2</sub>O<sub>9</sub>).

20 (2) Synthesis of 12-[2'-(N-tBOC-glutamic acid)- α -amide]deoxoartemisinin (IX).

12-[2'-(N-tBOC-glutamic- γ -benzylester)- α -amide]deoxoartemisinin (VIII)(36mg, 0.057mmol) was dissolved in dry THF/H<sub>2</sub>O(1/1, 5mL) and 1N LiOH(1mL) was added. The solution was allowed to stir at room temperature for 2hours. The reaction solution 25 was acidified with 1N HCl, extracted with ethyl acetate (20mL x 3), and then washed with brine (10mL x 2). The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo, then purified by silica gel column (hexane/ethyl acetate = 1/2 as eluent) to afford 12-[2'-(N-tBOC-glutamic acid)- α -amide]deoxoartemisinin (IX)(26.8mg, 87%) as a colorless oil.

30 [α]<sup>25</sup><sub>D</sub> = +66.4 (c 0.34, CHCl<sub>3</sub>).

<sup>1</sup>H- NMR(CDCl<sub>3</sub>, 250MHz) δ5.60(d, 1H, J=7.9Hz, NH), 5.33(s, 1H, H-5), 4.34-4.32(m,

1H, H-12), 4.20-4.15(m, 1H), 3.49-3.47(m, 1H, H-2), 3.33-3.31(m, 1H, H-2), 2.66-2.58(m, 1H), 2.48-2.40(m, 2H), 2.30(ddd, 1H, J=2.2, 1.9, 3.7Hz), 2.03-1.73(m, 5H), 1.67-1.61(m, 6H), 1.41(s, 9H, *t*-BOC), 1.38(s, 3H, CH<sub>3</sub>-15), 1.33-1.21(m, 3H), 0.95(d, 3H, J=5.1Hz, CH<sub>3</sub>-13), 0.84(d, 3H, J=7.4Hz, CH<sub>3</sub>-14), 0.81(m, 1H).

5     <sup>13</sup>C-NMR ((CDCl<sub>3</sub>, 63MHz,) δ176.6, 172.2, 103.7, 89.7, 81.4, 76.9, 74.7, 53.4, 52.5, 44.3, 39.1, 37.8, 36.8, 34.7, 30.7, 30.6, 29.8, 28.7, 28.7, 28.7, 28.7, 26.2, 25.2, 25.0, 20.5, 13.0. IR(neat) ν<sub>max</sub> 3352(CO<sub>2</sub>H and NH), 2933, 2879, 1714(C=O), 1657(C=O), 1533, 1459, 1379, 1275, 1170, 1053, 914, 882(O-O), 733 cm<sup>-1</sup>  
LCMS(ESI) m/z 540([M+]).

10

(3) Synthesis of 12-[2'-(N-*t*BOC-glutamic)- α , β -amide]deoxoartemisinin dimer (X).

12-[2'-(N-*t*BOC-glutamic acid)- α -amide]deoxoartemisinin (IX)(21mg, 0.039mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub>(2mL) and HOBr(22mg, 0.119mmol) and EDC(29mg, 0.119mmol) 15 were added together. The reaction mixture was allowed to stir at room temperature for 30 minutes and 12-(2'-aminoethyl)deoxoartemisinin (VI)(18mg, 0.058mmol) was added. The resulting reaction mixture was allowed to stir at room temperature for 3hours. The reaction mixture was extracted with ethyl acetate (20mL x 3) and washed with brine (10mL x 2). The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo, then purified by silica 20 gel column (hexane/ethyl acetate = 1/2 as eluent) to afford 12-[2'-(N-*t*BOC-glutamic)- α , β -amide]deoxoartemisinin dimer (X)(16.6mg, 51 %) as a colorless oil.

[α]<sup>25</sup><sub>D</sub> = +114.6(c 0.46, CHCl<sub>3</sub>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz) δ6.71(s, 1H, NH), 5.87(s, 1H, NH), 5.34(s, 1H, H-5), 5.33(s, 1H, H-5), 4.34-4.31(m, 2H, H-12), 4.13-4.10(m, 1H), 3.53-3.48(m, 2H), 3.25-3.23(m, 2H), 2.62-2.60(m, 2H), 2.39-2.29(m, 6H), 2.05-1.88(m, 8H), 1.86-1.62(m, 12H), 1.43(s, 9H, *t*-BOC), 1.39(s, 6H, CH<sub>3</sub>-15), 1.28-1.25(m, 5H), 0.96(d, 6H, J=5.3Hz, CH<sub>3</sub>-13), 0.86(d, 6H, J=7.5Hz, CH<sub>3</sub>-14), 0.83(m, 2H).

25     <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63MHz,) δ173.3, 173.2, 171.5, 171.4, 103.5, 103.4, 89.8, 89.6, 81.4, 81.4, 76.9, 74.3, 52.5, 52.5, 44.4, 44.3, 39.3, 37.8, 36.8, 34.7, 30.8, 28.9, 28.7, 26.4, 25.2, 25.1, 20.5, 14.5, 13.0, 12.8.

30     IR(neat) ν<sub>max</sub> 3379(NH), 2877, 1713(C=O), 1656(C=O), 1545, 1451, 1379, 1268, 1030,

917, 880(O-O), 732 cm<sup>-1</sup>

LCMS(ESI) m/z 834([M+H]).

(4) Synthesis of the title compound.

5

12-[2'-(N-tBOC-glutamic)- α ,β -amide]deoxoartemisinin dimer (X) (28mg, 0.036mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub>(2mL). To this solution was slowly added TFA(4.92mg, 1.2eq) at 0 °C for 30 minutes. The resulting reaction mixture was allowed to stir at 0 °C for 4hours, extracted with ethyl acetate (20mL x 3) and washed with brine (10mL x 2).

10 The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo, then purified by silica gel column (hexane/ethyl acetate = 1/2 as eluent) to afford 12-[2'-(N-glutamic)- α ,β -amide]deoxoartemisinin dimer (IVd)(19mg, 72 %) as a colorless oil. The dimer (IVd) is five times more water soluble (5.21 mg/ml) than artemisinin.

[α]<sup>25</sup><sub>D</sub> = +120.8 (c 0.48, CHCl<sub>3</sub>).

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz) δ6.83(s, 1H, NH), 5.74(s, 1H, NH), 5.34(s, 1H, h-5), 5.31(s, 1H, H-5), 4.35-4.33(m, 2H, H-12), 4.15-4.12(m, 1H), 3.53-3.49(m, 2H), 3.27-3.24(m, 2H), 2.64-2.62(m, 2H), 2.32-2.30(m, 2H), 2.15-1.58(m, 12H), 1.53-1.41(m, 10H), 1.39(s, 6H, CH<sub>3</sub>-15), 1.34-1.28(m, 6H), 0.97(d, 6H, J=5.3Hz, CH<sub>3</sub>-14), 0.86(d, 6H, J=7.5Hz, CH<sub>3</sub>-14), 0.82(m, 2H).

20 <sup>13</sup>C-NMR (63MHz, CDCl<sub>3</sub>) δ173.4, 173.3, 171.5, 171.3, 103.6, 103.4, 89.8, 89.7, 84.4, 84.3, 76.9, 74.3, 52.6, 52.4, 44.5, 44.3, 39.3, 37.9, 36.7, 34.6, 30.9, 30.8, 28.7, 26.4, 25.2, 25.1, 20.5, 20.4, 14.5, 13.3, 12.7.

IR(neat) ν<sub>max</sub> 3367(NH), 3098(NH), 2956, 2868, 1689(C=O), 1558, 1446, 1380, 1209, 1137, 998, 887(O-O), 847, 757, 729 cm<sup>-1</sup>

25 HRMS(FAB) m/z 734.4592([M+H]<sup>+</sup>, obsd), 733.4513(calc for C<sub>39</sub>H<sub>63</sub>N<sub>3</sub>O<sub>10</sub>). Elemental analysis (C<sub>39</sub>H<sub>63</sub>N<sub>3</sub>O<sub>10</sub>) C, H, N.

**Example 9: Synthesis of deoxoartemisinin trimer (IVe).**

30 (1) Synthesis of N-[12-(β -deoxoartemisinin)propionyl]-L-glutamic diethyl ester (XI).

12-carboxylethyldeoxoartemisinin (VII)(32mg, 0.256mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub>(3mL) and HOBr(38mg, 0.256mmol) and EDC(47mg, 0.256mmol) were added together. The reaction mixture was allowed to stir at room temperature for 30 minutes and L-glutamic diethylester (36mg, 0.171mmol) was added. The resulting reaction  
5 mixture was allowed to stir at room temperature for 3hours. The reaction mixture was extracted with ethyl acetate (20mL x 3) and washed with brine (10mL x 2). The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo, then purified by silica gel column (hexane/ethyl acetate = 1/2 as eluent) to afford N-[12-( $\beta$ -deoxoartemisinin)propionyl]-L-glutamic diethylester (XI) (37.9mg, 84%) as a colorless  
10 oil.

[ $\alpha$ ]<sup>25</sup><sub>D</sub> = +44.5 (c 0.47, CHCl<sub>3</sub>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz,)  $\delta$  6.31(d, 1H, J=7.5Hz, NH), 5.29(s, 1H, H-5), 4.63-4.56(m, 1H), 4.23-4.08(m, 5H), 2.75-2.71(m, 1H), 2.50-2.18(m, 7H), 2.04-1.65(m, 9H), 1.40(s, 3H, CH<sub>3</sub>-15), 1.31(s, 3H), 1.28(s, 3H), 1.22-1.15(m, 2H), 0.96(d, 3H, J=5.8Hz, CH<sub>3</sub>-13),  
15 0.88(d, 3H, J=7.5Hz, CH<sub>3</sub>-14), 0.85(m, 1H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63MHz)  $\delta$  173.2, 172.3, 103.7, 89.1, 81.5, 76.8, 76.3, 61.9, 61.0, 52.7, 52.0, 44.8, 37.7, 36.8, 34.8, 34.8, 31.2, 30.7, 30.5, 27.8, 26.4, 25.2, 25.0, 20.5, 14.5, 13.5.  
IR(neat)  $\nu$ <sub>max</sub> 3370(NH), 2939, 2878, 1737(C=O), 1669(C=O), 1533, 1446, 1372, 1054,  
1012, 880(O-O), 742 cm<sup>-1</sup>

20 MS(FAB) m/z 526.5([M+H]<sup>+</sup>).

Elemental analysis (C<sub>27</sub>H<sub>43</sub>NO<sub>9</sub>) C, H, N.

(2) Synthesis of N-[12-( $\beta$ -deoxoartemisinin)propionyl]-L-glutamic diacid(XII).

25

N-[12-( $\beta$ -deoxoartemisinin)propionyl]-L-glutamic diethylester (XI)(2mg, 0.08mmol) was dissolved in THF/H<sub>2</sub>O(1/1, 5mL), 1N LiOH(1mL) was added and then was allowed to stir at room temperature for 2hours. To the reaction mixture was added 1N HCl(1mL). The resulting reaction mixture was extracted with ethyl acetate (20mL x 3) and washed with  
30 brine (10mL x 2). The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo, then purified by silica gel column (hexane/ethyl acetate = 1/2 as eluent) to afford N-[12-( $\beta$

-deoxoartemisinin)propionyl]-L-glutamic diacid (XII)(30.8mg, 82%) as a colorless oil.  
[ $\alpha$ ]<sup>26</sup><sub>D</sub> = +76.8 (c 0.22, CHCl<sub>3</sub>).

m.p. 106 °C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz) δ8.96(br, 2H, CO<sub>2</sub>H), 7.08(d, 1H, J=6.5Hz, NH), 5.34(s, 1H, H-5), 4.62-4.60(m, 1H), 4.12-4.04(m, 1H, H-12), 2.72-2.70(m, 1H), 2.48-2.26(m, 6H), 2.08-1.98(m, 3H), 1.82-1.78(m, 3H), 1.71-1.42(m, 4H), 1.41(s, 3H, CH<sub>3</sub>-15), 1.27-1.21(m, 2H), 0.95(d, 3H, J=5.3Hz, CH<sub>3</sub>-13), 0.87(d, 3H, J=7.2Hz, CH<sub>3</sub>-14), 0.84(m, 1H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63MHz) δ177.3, 176.6, 175.1, 174.7, 104.3, 89.0, 81.5, 76.9, 52.8, 52.1, 44.9, 37.6, 36.8, 34.8, 34.5, 30.4, 27.1, 26.2, 25.1, 24.9, 21.0, 20.6, 13.7.

IR(KBr)  $\nu_{max}$  3346(CO<sub>2</sub>H), 2942, 2877, 1728(C=O), 1631(C=O), 1539, 1453, 1381, 1202, 1051, 912, 880(O-O), 732 cm<sup>-1</sup>  
LCMS(ESI) m/z 492 ([M+Na]<sup>+</sup>).

Elemental analysis (C<sub>23</sub>H<sub>35</sub>NO<sub>9</sub>) C, H, N.

15

(3) Synthesis of the title compound.

N-[12-( $\beta$ -deoxoartemisinin)propionyl]-L-glutamic diacid (XII)(22mg, 0.047mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub>(2mL) and HOBr(27mg, 0.141mmol) and EDC(31mg, 0.141mmol) were added. The reaction mixture was allowed to stir at room temperature for 30 minutes and 12-(2'-aminoethyl)deoxoartemisinin (VI)(29mg, 0.093mmol) was added. The resulting reaction mixture was allowed to stir at room temperature for 19hours. The reaction mixture was extracted with ethyl acetate (30mL x 3) and washed with brine (20mL x 2). The extract was dried over MgSO<sub>4</sub>, concentrated in vacuo, then purified by silica gel column (hexane/ethyl acetate = 1/2 as eluent) to afford deoxoartemisinin trimer (IVe)(73.3mg, 74%) as a colorless solid.

[ $\alpha$ ]<sup>24</sup><sub>D</sub> = +102.7 (c 0.41, CHCl<sub>3</sub>).

m.p. 138 °C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz) δ7.13-7.04(m, 2H, NH), 6.83-6.81(m, 1H, NH), 5.32(s, 2H, H-5), 5.29(s, 1H, H-5), 4.39-4.34(m, 3H, H-12), 4.29-4.26(m, 1H), 3.55-3.48(m, 2H), 3.32-3.27(m, 2H), 2.65-2.63(m, 3H), 2.36-2.31(m, 7H), 2.17-1.93(m, 11H), 1.91-1.51(m,

17H), 1.39(s, 9H, CH<sub>3</sub>-15), 1.33-1.21(m, 7H), 0.95(d, 9H, J=5.4Hz, CH<sub>3</sub>-13), 0.88-0.83(m, 9H, CH<sub>3</sub>-14), 0.82(m, 3H).

13C-NMR (CDCl<sub>3</sub>, 63MHz) δ174.4, 174.3, 173.2, 173.1, 103.5, 103.4, 89.9, 89.8, 81.5,  
5 81.4, 76.8, 53.2, 53.1, 52.8, 52.6, 52.4, 37.7, 36.8, 34.7, 31.3, 30.8, 30.7, 30.0, 29.1, 26.4,  
26.4, 25.1, 20.5, 20.4, 13.2, 13.1.

IR (KBr) ν<sub>max</sub> 3308(NH), 2933, 2875, 1667(C=O), 1535, 1465, 1377, 1102, 1061, 1014,  
938, 874(O-O), 751 cm<sup>-1</sup>

HRMS (FAB) m/z 1056.6392([M+H]<sup>+</sup>, obsd), 1055.6294(calcd for C<sub>57</sub>H<sub>89</sub>N<sub>3</sub>O<sub>15</sub>).

10 Elemental analysis (C<sub>57</sub>H<sub>89</sub>N<sub>3</sub>O<sub>15</sub>) C, H, N.

**Example 10: Synthesis of 12-(4'-aminobutyl)deoxoartemisinin (VI').**

(1) Synthesis of 12-(4'-butyl azide)deoxoartemisinin.

15

12-(4'-butyl azide)deoxoartemisinin (116.9mg, 92%) was prepared as a colorless oil by  
following the procedure of Example 2 (1), but replacing  
12-(2'-bromoethyl)deoxoartemisinin with 12-(4'-bromobutyl)deoxoartemisinin (137.9mg,  
0.352mmol).

20

[α]<sup>24</sup><sub>D</sub> = +71.3 (c 0.1, CHCl<sub>3</sub>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz) δ5.29(s, 1H, H-5), 4.19-4.12(m, 1H, H-12), 3.26(t, 2H,  
J=6.6Hz, H-4), 2.64-2.62(m, 1H), 2.31(ddd, 1H, J=4.1, 3.8, 4.1Hz), 2.04-1.89(m, 2H),  
1.68-1.65(m, 2H), 1.63-1.58(m, 7H), 1.40(s, 3H, CH<sub>3</sub>-15), 1.34-1.22(m, 4H), 0.96(d, 3H,  
25 J=5.7Hz, CH<sub>3</sub>-13), 0.86(d, 3H, J=7.5Hz), 0.82(m, 1H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63MHz), δ103.4, 89.4, 81.4, 75.3, 52.6, 51.7, 44.6, 37.7, 36.9, 34.7,  
30.6, 29.3, 29.0, 26.4, 25.2, 25.0, 25.0, 20.5, 13.2.

IR (neat) ν<sub>max</sub> 2927, 2876, 2095(N<sub>3</sub>), 1597, 1454, 1379, 1255, 1097, 1012, 946, 881(O-O),  
643 cm<sup>-1</sup>

30 MS (FAB) 366.4([M+H]<sup>+</sup>).

## (2) Synthesis of the title compound.

12-(4'-aminobutyl)deoxoartemisinin (VI')(94.3mg, 79%) was prepared as a white solid by following the procedure of Example 2 (2), but replacing 12-(2'-ethyl azide)deoxoartemisinin with 12-(4'-butyl azide)deoxoartemisinin (128.8mg, 0.352mmol).

$[\alpha]^{25}_D = +49.4$  (c 0.1, CHCl<sub>3</sub>).

m.p. 105 °C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz) δ5.29(s, 1H, H-5), 4.16-4.09(m, 1H, H-12), 2.71-2.66(m, 3H), 2.32(ddd, 1H, J=4.1, 3.8, 4.1Hz), 2.08-2.04(m, 2H), 1.87-1.72(m, 3H), 1.66-1.53(m, 4H), 1.51-1.45(m, 4H), 1.41(s, 3H, CH<sub>3</sub>-15), 1.36-1.24(m, 4H), 0.96(d, 3H, J=4.3Hz), 0.86(d, 3H, J=7.5Hz), 0.83(m, 1H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63MHz), δ103.5, 89.4, 81.5, 76.0, 52.6, 51.8, 44.8, 38.4, 36.9, 34.8, 31.2, 29.4, 29.0, 26.5, 25.3, 25.2, 25.1, 20.5, 13.3.

IR(KBr)  $\nu_{max}$  3378(NH), 2925, 1591, 1454, 1379, 1117, 1038, 1005, 887(O-O), 748 cm<sup>-1</sup>  
HRMS(FAB) m/z 340.2402([M+H]<sup>+</sup>, obsd), 339.2410(calcd for C<sub>19</sub>H<sub>33</sub>NO<sub>4</sub>).

Elemental analysis (C<sub>19</sub>H<sub>33</sub>NO<sub>4</sub>) C, H, N.

**Example 11: Synthesis of 12-(4'-aminobutyl)deoxoartemisinin dimer(IVc').**

20

12-(4'-aminobutyl)deoxoartemisinin dimer (IVc')(46mg, 81%) was prepared as a colorless oil by following the procedure of Example 7, but replacing 12-(2'-aminoethyl)deoxoartemisinin with 12-(4'-aminobutyl)deoxoartemisinin (28mg, 0.096mmol).

25

$[\alpha]^{23}_D = +104.2$  (c 0.23, CHCl<sub>3</sub>).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250MHz) δ5.68(s, 1H, NH), 5.28(s, 2H, H-5), 4.13-4.03(m, 2H, H-12), 3.25-3.21(m, 2H, H-4), 2.72-2.65(m, 2H), 2.39-2.21(m, 4H), 2.11-1.67(m, 9H), 1.61-1.46(m, 10H), 1.40(s, 6H, CH<sub>3</sub>-15), 1.36-1.22(m, 7H), 0.96(d, 6H, J=4.6Hz, CH<sub>3</sub>-13), 0.89(d, 3H, J=7.4Hz, CH<sub>3</sub>-14), 0.86(d, 3H, J=7.4Hz, CH<sub>3</sub>-14), 0.83(m, 2H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63MHz) δ 173.3, 126.5, 126.3, 118.2, 112.5, 103.7, 103.6, 89.4, 89.1, 81.5, 76.9, 76.4, 75.9, 52.8, 52.5, 44.8, 44.3, 37.8, 37.0, 36.4, 36.1, 35.2, 35.1, 34.8, 34.3, 30.6, 30.6, 26.6, 26.4, 25.2, 25.1, 25.1, 25.1, 20.6, 20.5, 13.7, 13.6.

IR(neat) ν<sub>max</sub> 3388(NH), 2936, 2875, 1650(C=O), 1539, 1452(C-N), 1379, 1216, 1097, 1051, 1005, 873(O-O), 753 cm<sup>-1</sup>

HRMS(FAB) m/z 662.4173([M+H]<sup>+</sup>, obsd), 661.4190(calcd for C<sub>37</sub>H<sub>59</sub>NO<sub>9</sub>).

Elemental analysis (C<sub>37</sub>H<sub>59</sub>NO<sub>9</sub>) C, H, N.

#### Example 12: Measurement of anticancer activity.

10

The anticancer activities of the deoxoartemisinin dimer and trimer of the present invention were measured by a known micro-culture tetrazolium assay (see Carmichel, J.; DeGraff, W. G.; Gazdar, A. F.; Minna, J. D.; Mitchell, J. B., Evaluation of a Tetrazolium-based Semiautomated Colorimetric Assay: Assessment of Chemosensitivity testing, *Cancer Res.*, 1987, 47, 936-42).

The table 1 shows cytotoxicities of the compounds of the present invention on mouse and human cancer cells *in vitro*.

20 Table 1

*In vitro* cytotoxicities (IC<sub>50</sub> (μg/mL))

	P388	EL4	Bewo	HT-29	PANC-1	SKOV3	MCF7	A549
Compound (IVa <sub>1</sub> )	0.40	0.23	14.20	0.24			0.017	
Compound (IVa <sub>2</sub> )	5.60	0.54	1.04	0.38			0.025	
Compound (IVb)	8.40	10.00	8.50	0.38			5.6	
Compound (IVc)	10.40	6.29	7.50	0.69		12.6	0.005	
Compound (IVc')	>20	>20	>20	20.20			>20	
Compound (IVd)	15.60	16.50	>20	6.50			15.3	
Compound (IVe)	0.12	1.07	18.30	0.09	2.69	11.2	0.017	2.45
Adriamycin	0.39	0.67	6.24	0.10			0.12	
Mitomycin	1.50	3.94	0.85	0.02			0.93	1.85

Taxol	2.27	1.34	7.39	0.01	5.76	12.30	0.0001	
-------	------	------	------	------	------	-------	--------	--

P388: mouse fibroblast leukemia cell

EL4: mouse thymoma cell

Bewo: human choriocarcinoma cell

HT-29: human colorectal adenocarcinoma cell

5 PANC-1: human pancreatic cancer cell

SKOV3: human ovarian carcinoma cell

MCF7: human breast carcinoma cell

A549: human lung cancer cell

- 10 As shown in Table 1, the sulfide dimer (IVa<sub>1</sub>) of the present invention exhibited an anticancer activity on the mouse fibroblast leukemia cell (P388), said activity being comparable to that of adriamycin and being at least 4-fold higher than that of mitomycin. Also, the trimer (IVe) of the present invention exhibited an anticancer activity on P388, said activity being at least 3-fold higher than that of adrimycin, at least 12-fold higher than that of mitomycin and at least 20-fold higher than that of taxol. The sulfide dimer (IVa<sub>1</sub>), sulfone dimer (IVa<sub>2</sub>) and trimer (IVe) of the present invention exhibited an anticancer activity on the mouse thymoma cell (EL4), said activity being comparable to that of adriamycin. Most compounds had little anticancer activity on human choriocarcinoma cell (Bewo) but the sulfone dimer (IVa<sub>2</sub>) had an anticancer activity on Bewo, which was comparable to that of mitomycin and was at least 6-fold higher than that of taxol and adriamycin. The trimer (IVe) of the present invention exhibited an anticancer activity on human colorectal adenocarcinoma cell (HT-29), said activity being comparable to that of adriamycin, and also exhibited an anticancer activity on human pancreatic cancer cell, said activity being at least 2-fold higher than that of taxol. Most compounds had little anticancer activity on human ovarian carcinoma cell (SKOV3), while the amide dimer (IVc) and trimer (Ive) of the present invention had an anticancer activity similar to that of taxol. The amide dimer (IVc), sulfide dimer (IVa<sub>1</sub>), sulfone dimer (IVa<sub>2</sub>) and trimer (IVe) had higher anticancer activity on human breast carcinoma cell (MCF7). Especially, the amide dimer (IVc) of the present invention exhibited an anticancer activity on MCF7, said activity being at least 24-fold higher than that of adriamycin and at least 200-fold higher than that of mitomycin. Most of the compounds had less anticancer activity on human

lung cancer cell (A549), while the trimer (IVe) of the present invention had an anticancer activity on A549 similar to that of mitomycin.

From the results, it can be seen that the trimer (IVe) of the present invention has a very excellent anticancer activity on most mouse and human cancer cells. Also, it can be seen that the anticancer activity of the dimer of the present invention depends on the length of the linker located between two deoxoartemisinins. In other words, the compounds (IVa<sub>1</sub>), (IVa<sub>2</sub>) and (IVc), in which a linker has one amide- or one sulfur-centered two ethylene groups, have superior anticancer activity to the compounds (IVa<sub>1</sub>), (IVa<sub>2</sub>) and (IVc), in which a linker is longer than the length of two ethylene groups.

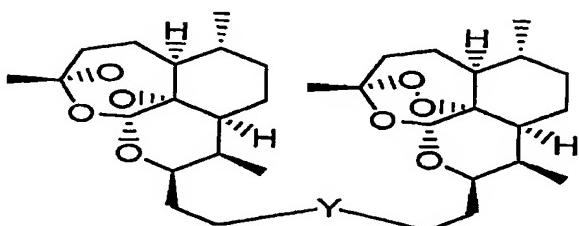
#### INDUSTRIAL APPLICABILITY

The deoxoartemisinin dimer and trimer of the present invention are C-12 non-acetal-type and do not have linker containing C-O bonds, aromatic or unsaturated groups at C-12 positions, and thus are acid stable, less toxic and have higher anticancer activity.

Also, according to the preparation of the present invention, the deoxoartemisinin analog is easily prepared in high yield.

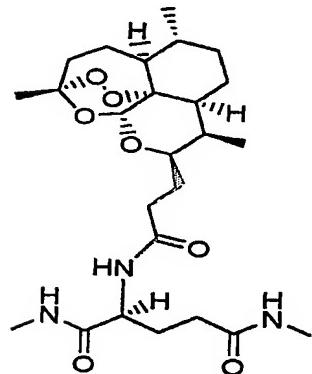
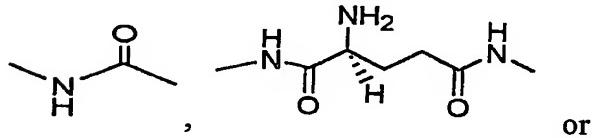
**Claims**

1. A deoxoartemisinin analog of the following formula:

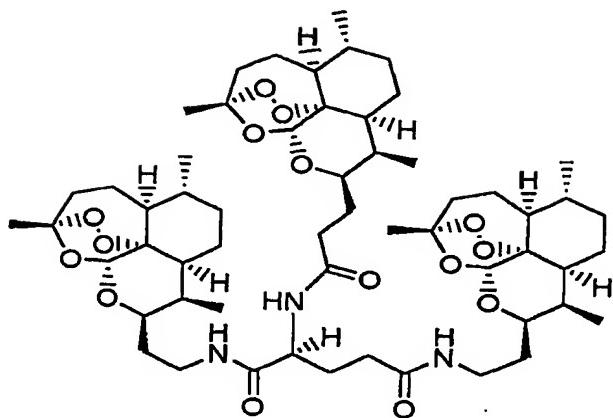


5

wherein Y is -S-, -SO<sub>2</sub>-, -S-CH<sub>2</sub>-CH<sub>2</sub>-S-, or -S(=O)<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-S(=O)<sub>2</sub>,

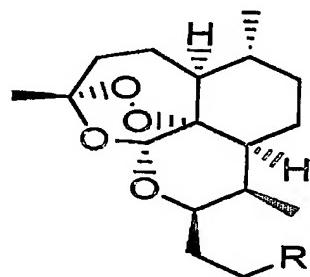


2. A method for preparing deoxoartemisinin trimer of the following formula, said method comprising the steps of: (a) coupling 12-carboxylethyldeoxoartemisinin with L-glutamic diethylester; (b) hydrolyzing two ester groups of the product from said step (a); and (c) doubly coupling the product from said step (b) with 2 moles of 12-aminoethyldeoxoartemisinin:



3. The method as claimed in claim 2, wherein said coupling reaction is carried in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and  
5 10-hydroxybenzotriazole (EDC/HOBt).

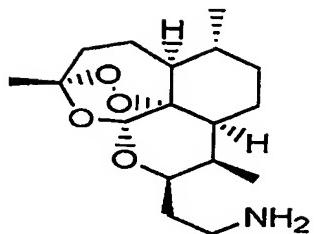
4. A deoxoartemisinin analog of the following formula:



wherein R is Br or NH<sub>2</sub>.

10

5. A method for preparing 12-aminoethyldeoxoartemisinin of the following formula, said method comprising the steps of: (a) hydroborative oxidizing a terminal olefin of 12-vinyldihydroartemisinyl alcohol; (b) brominating the product from said step (a) with CBr<sub>4</sub>/PPh<sub>3</sub>; (c) photoxygenative cyclizing the product from said step (b); (d) reacting the  
15 product from said step (c) with sodium azide; and (e) reducing an azide group of the product from said step (d):



6. An anticancer agent comprising said deoxoartemisinin analog as claimed in claim 1.

5

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/KR2004/000086

## A. CLASSIFICATION OF SUBJECT MATTER

**IPC7 C07D 493/22**

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

**IPC7 C07D 493/22**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
Korean Patents and applications for inventions since 1975.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
**STN(CASLINK)**

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OGNYANOV et. al., 'Synthesis and antimalarial activity of novel C12-ethers of 11-hydroxydihydroartemisinin' In: Dokladi na Bulgarskata Akademiya na Naukite (CODEN: DBANEH. ISSN: 0861-1459), 1993, 46(11), pp. 45-48	4
P, X	JUNG et. al., 'Antitumor activity of novel deoxoartemisinin monomers, dimers, and trimer' In: Journal of Medicinal Chemistry, 13 March 2003 , 46(6), pp. 987-994	1 - 6
A	WO 9308195 A1 (The University of Sydney) 29 April 1993, see entire document.	1 - 6

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier application or patent but published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search

08 MAY 2004 (08.05.2004)

Date of mailing of the international search report

12 MAY 2004 (12.05.2004)

Name and mailing address of the ISA/KR



Korean Intellectual Property Office  
920 Dunsan-dong, Seo-gu, Daejeon 302-701,  
Republic of Korea

Faxsimile No. 82-42-472-7140

Authorized officer

LEE, Jac Jeong

Telephone No. 82-42-481-5604



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2004/000086

Patent document  
cited in search report

Publication  
date

Patent family  
member(s)

Publication  
date

WO 9308195 A1

29-04-1993

JP 7500325 T2  
AU 2767292 A1

12-01-1995  
21-05-1993